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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,036	12/10/2001	Michel Koehl	017753-150	8634

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EXAMINER	
CHEN, STACY BROWN	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,036	KOEHL ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-38* is/are rejected.

7)☒ Claim(s) *35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 27, 2004 has been entered.

Response to Amendment

2. The objections to claims 19 and 32 are withdrawn in view of Applicant's amendment correcting minor informalities. The rejection of claims 20, 21, 35 and 38 under 35 U.S.C. 112, second paragraph, is withdrawn in view of Applicant's amendment removing trademarks and clarifying the identity of the types of matrices in claims 20 and 21.

Claim Objections

3. Claim 35 is objected to for misspelling "methylene".

Claim Rejections - 35 USC § 103

4. The rejection of claims 19-38 under 35 U.S.C. 103(a) as unpatentable over Shabram *et al.* (WO 96/27677 A2), herein, "Shabram", in view of Berg (WO 98/33572 A1) is withdrawn in view of Applicant's amendment. However, the following new rejection is applied.

Claims 19-38 are rejected under 35 U.S.C. 103(a) as unpatentable over Shabram, in view Bondoc *et al.* (*J. Indust. Micro. & Biotech.*, 1998, 20:317-322), herein "Bondoc" and Berg. The

amended claims are drawn to a method for purifying adenoviral particles from a crude viral preparation comprising a fluidized bed chromatography step followed by a gel filtration chromatography step. The adsorbent used in the fluidized bed step comprises an agarose matrix and a central core comprising quartz, and dextran chains covalently coupled to said agarose matrix, on which are attached positively charged groups. The limitations of the dependent claims have been summarized in previous Office actions.

The teachings of Shabram are of record. To summarize, Shabram teaches a method of purifying recombinant adenoviruses (viral vectors for use in gene therapy) from a cell lysate comprising two chromatography steps (fluidized-bed adsorption followed by immobilized metal affinity column (IMAC) or hydrophobic interaction chromatography (HIB)), see abstract, page 4, lines 5-10, page 8, lines 4-8, and page 9, lines 13-15. Shabram uses a cross-linked agarose column (page 11, lines 27-28). The salt concentration of the eluant is diluted to about 450 millimolar or less in order to prevent premature stripping of viral particles from the exchange resin (page 12). A buffer is used to maintain the pH of the cell lysate solution between about 5.0 and 9.0. During chromatography, the resins are treated by flushing with NaCl and water. Shabram also discloses the production of adenoviral vectors from cell lines (page 15), lysis (page 17) and nucleic acid degradation (page 18). Shabram fails to teach the step of gel filtration, the specific type of adsorbent particle as instantly claimed, and the overall yield of approximately 80% or higher.

Bondoc teaches a method of purifying recombinant adenovirus (rAd5) using size exclusion chromatography, also called gel filtration (page 318, first column, third full paragraph).

Berg teaches a method for adsorption of a substance from a liquid sample on a fluidized bed, in which the total yields are improved. The beads used in the method comprise a structure/ligand linked to a base matrix (bead) via an extender. The base matrix is comprised of cross-linked agarose (page 8, lines 28-33) and a bead filler of quartz (page 9, lines 30-31). Dextran is covalently bound to the agarose matrix (page 5, lines 2-17).

It would have been obvious to modify Shabram's method by substituting Bondoc's step of gel filtration with Shabram's step of IMAC. One would have been motivated by Bondoc's teaching that gel filtration chromatography can be substituted for zinc metal-chelating chromatography, a form of IMAC (page 318, first column, third full paragraph). One would have had a reasonable expectation of success that the gel filtration step would have resulted in purified adenoviruses because Bondoc reports that the adenovirus particles obtained by gel filtration were comparable with those obtained with the standard cesium chloride (CsCl) gradient-method page 318, first column, third full paragraph). It would have been obvious to use the adsorbent particles taught by Berg in Shabram's method. One would have been motivated to use Berg's adsorbent particles because Berg's method is aimed at improving total yields and productivity in adsorption processes on fluidized beds, and providing filler matrices that have improved breakthrough capacity in fluidized beds (page 4, lines 15-21). One would have had a reasonable expectation of success that the adsorbent particles of Berg would have improved Shabram's method because Berg's adsorbent particles are intended for use in methods of adsorption using fluidized beds. Further, one would have expected that using Berg's adsorbent particles in the combined method of Shabram and Bondoc would have resulted in an improved yield over Shabram's 67%.

Applicant's substantive arguments are primarily directed to the following:

- While Shabram mentions the use of fluidized bed columns, only conventional packed bed columns (gravity) are used in the examples. Even if Shabram was suggesting the use of fluidized bed columns, the surprisingly better results (particle yields) were not appreciated. Shabram's method yields only 67%, which is 16% less than Applicant's yield using a fluidized bed column.
    - In response, Shabram clearly suggests the use of fluidized bed columns. Even though fluidized bed columns were not used in any of Shabram's examples, it was clearly suggested (page 9, line 15) and therefore an obvious choice. Regarding the yield, Applicant is claiming an approximately 80% or higher yield. The 67% yield of Shabram is encompassed by "approximately 80%" yield, since the term "approximately" is subject to individual interpretation and does not set forth a lower boundary. Further, one would have had a reasonable expectation of success that the combined methods of Shabram, Bondoc and Berg would have resulted in a higher yield than Shabram's 67%.
- Berg teaches against the present invention by indicating that in fluidized bed chromatography "[T]here is normally no upper limit in molecular weight, even though the process is normally limited to adsorption/separation of compounds that have a molecular weight below 1,000,000", page 12, lines 13-16. Shabram and Huyghe *et al.* (*Human Gene Therapy*, 1995, 6:1403-1416), herein, "Huyghe", teach that the molecular weight (MW) of a virus particle is about $2x10^8$. Applicant concludes from these

teachings that one would not be motivated to use fluidized bed chromatography for virus separation, since virus particles are much larger that the MW limit taught by Berg.

- In response, Berg is not precluding the use of fluidized bed chromatography for separating viruses. Berg is merely disclosing that fluidized bed chromatography is *usually* limited to compounds having a MW<1,000,000, but that it does not normally have an upper limit. This teaching is not discouraging the use of fluidized bed chromatography for compounds having a MW>1,000,000, such as virus particles.

Conclusion

5. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SBC
Stacy B. Chen
July 7, 2004

James C. Housel 7/12/04
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